SYNTHESIS OF (±)-ISOCORYTUBERINE AND (±)-N-METHYLISOCORYTUBERINE

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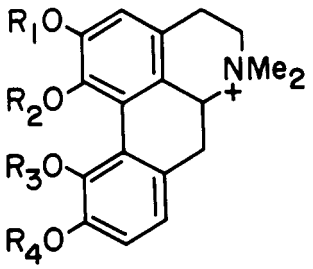
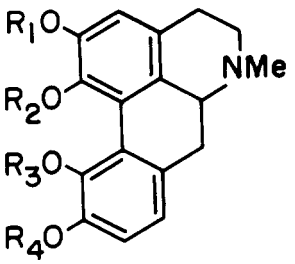
ABSTRACT.—The first directed syntheses of (±)-isocorytuberine and (±)-*N*-methylisocorytuberine are reported. *N*-methylisocorytuberine is an isomer of magnoflorine and *N,N*-dimethyllindcarpine and its spectral properties were compared with those of the latter two alkaloids. The data show that both tlc and spectral differences easily distinguish between *N*-methylisocorytuberine and magnoflorine. On the other hand, comparative data indicate that more care is necessary to distinguish between isocorytuberine and *N*-methyllindcarpine and between their quaternary methiodides.

The quaternary aporphine alkaloid magnoflorine (**1**) is ubiquitous in some plant families and would be a strong candidate for the alkaloid of most widespread occurrence in all plants. On the other hand, its isomers *N,N*-dimethyllindcarpine (**2**), *N,N*-dimethylhernovine (**3**), and *N*-methylisocorytuberine (**4**) appear to be unknown as natural products. We recently (1) cleared up confusion between **1** and **2** by preparation and comparison of authentic samples of each. In order to further insure that reports on the isolation of **1** could not be due to its other isomers, we have, for the first time, prepared *N*-methylisocorytuberine **4** and examined its spectral and tlc properties in comparison with those of **1** and **2**.



1 (magnoflorine): $R_1=R_4=Me$; $R_2=R_3=H$.
2 (N,N-dimethyllindcarpine): $R_1=R_3=H$; $R_2=R_4=Me$.
3 (N,N-dimethylhernovine): $R_1=R_4=H$; $R_2=R_3=Me$.
4 (N-methylisocorytuberine): $R_1=R_3=Me$; $R_2=R_4=H$.

Isocorytuberine (**5**) has only been prepared by a sequence involving nonspecific phenol oxidation of a tetrahydrobenzylisoquinoline, followed by reduction and acid-catalyzed rearrangement (2). This provided **5** in very small yield

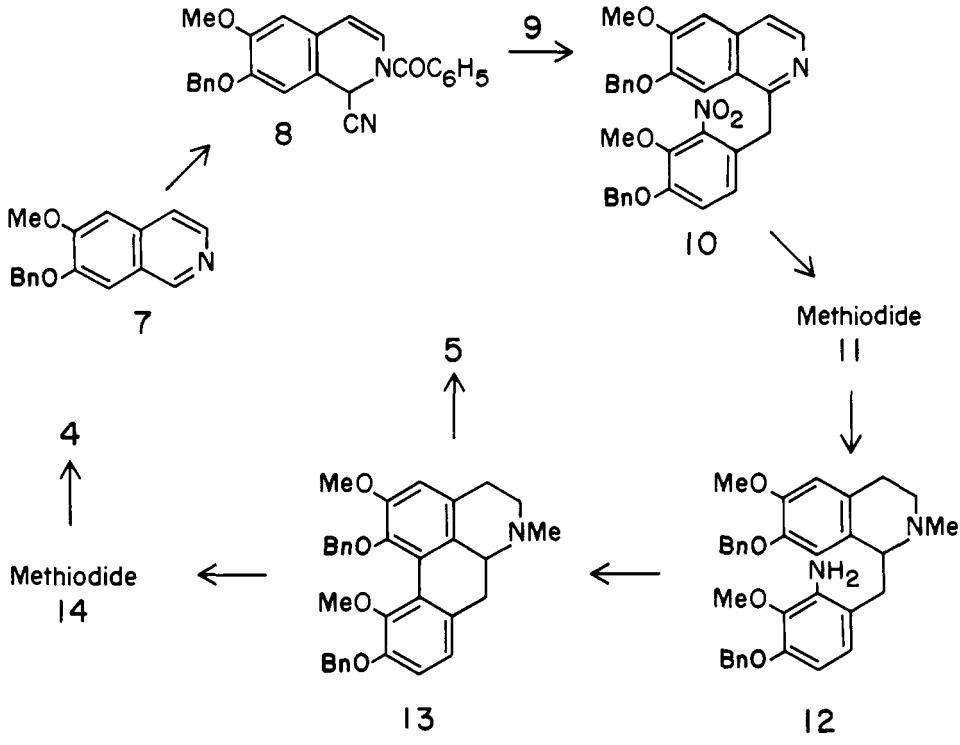


5 (isocorytuberine): $R_1=R_3=Me$; $R_2=R_4=H$.
6 (N-methyllindcarpine): $R_1=R_3=H$; $R_2=R_4=Me$.

along with other aporphine products, and the structure was established from chemical and spectral data. It was not, however, converted to **4**. Isocorytuberine was also unknown as a natural product until very recently when it was reported (3) from *Glaucium fimbrilligerum*. The structure was established by spectral comparisons with those quoted in the synthetic work (2), although correspondence was not exact for some of the ^{1}H nmr chemical shifts. Again, **5** was not converted to the quaternary methyl derivative **4**. Our preparation of **4** also made **5** available from an unequivocal synthesis.

RESULTS AND DISCUSSION

Details of the aporphine synthesis, which was accomplished by a sequence of Pomeranz-Fritsch, Reissert and Pschorr reactions (scheme 1), are given in the Experimental Section and in a thesis (4).



Scheme 1. Synthesis of Isocorytuberine and N-Methylisocorytuberine.

The ultraviolet and mass spectra of our isocorytuberine (**5**) matched those of the literature (2, 3). The ^{1}H nmr resonances (all in $CDCl_3$) are compared in table 1, along with data for *N*-methyllindcarpine (**6**). Our methyl resonances for **5** are virtually identical with those of Jackson and Martin (2), while a small

TABLE 1. ^{1}H Nmr values[a] for isocorytuberine and *N*-methyllindcarpine.

	(±)-5[b]	(±)-5[c]	(±)-5[d]	(±)-6[e]	(±)-6[f]
N-Me	2.56	2.58	2.51	2.58	2.51
O-Me	3.68	3.69	3.62	3.70	3.63
	3.91	3.93	3.84	3.97	3.89
Aromatics	6.66(s)	6.75(s)	6.61(s)	6.77(s)	6.68(s)
	6.85(d)	6.91(d)	6.75(d)	6.95(s, 2H)	6.81(s, 2H)
	7.01(d)	7.03(d)	6.93(d)		

[a]ppm, $CDCl_3$, 60 MHz. [b]This work. [c]Ref. 2. [d]Ref. 3. [e]A. Shafiee, I. Lalezari and O. Rahimi, *Lloydia*, **40**, 352 (1977). [f]L. Castedo, private communication, 80 MHz.

discrepancy remains for those of the natural material (3). Since all the deviations are in the same direction (higher field) for the natural substance, the discrepancies are probably artifactual. Resonances in the aromatic region for our **5** are intermediate to those of the other workers. We conclude that all represent the same material, with the exception that the natural material (3) was optically active. There is a rather remarkable closeness between the spectra of **5** and **6**, which only show a difference in the AA'BB' splitting of **5**, which is not observable with **6**. It is quite possible that if care is not taken to resolve the aromatic region of **5**, a false identification could be made.

Spectral and tlc data for *N*-methylisocorytuberine iodide (**4**) are given in table 2. Tlc data in both solvents clearly distinguishes it from magnoflorine

TABLE 2. Physical and spectral data for (±)-*N*-methylisocorytuberine iodide.

R_f 7:7:4:1 (MeOH/$CHCl_3$/$HCONH_2$/H_2O)	0.50
15:3:1 (MeOH/H_2O/HN_4OH)	0.08
Tlc visualization (short wave length uv)	dark, purple-black with no fluorescence
(long wave length uv)	light blue fluorescence at high concentration
UV, EtOH	227, 267, 273, 307
UV, EtOH, OH^-	223, 243, 279sh, 341
^1H nmr DMSO-d_6 (100 MHz)	NMe: 2.89, 3.35
	OMe: 3.63, 3.81
	Aromatics: 6.88 (s, 1H), 6.91 (s, 2H)
D_2O (60 MHz)	NMe: 2.68, 3.23
	OMe: 3.45, 3.87
	Aromatics: 6.60 (s, 2H), 6.83 (s, 1H)
CD_3OD (60 MHz)	NMe: 2.57, 3.37
	OMe: 3.62, 3.92
	Aromatics: 6.90 (m, 3H)

(**1**), while only the methanol-water-ammonium hydroxide solution solvent easily separates **4** from *N*,*N*-dimethyllindcarpine (**2**) (1). As was the case with the corresponding nonquaternary derivative **5** and **6**, the ^1H nmr resonances for the *N*- and *O*-methyls in DMSO at 100 MHz for **4** and **2** are virtually identical. Only in the aromatic region is a distinction possible. In this case, it is the *N*,*N*-dimethyllindcarpine which shows the expected AA'BB' splittings for the lower aromatic ring protons, while they are magnetically equivalent in *N*-methylisocorytuberine. The base shift in the uv spectrum may provide another distinguishing difference between **4** and **2**. The base-shifted peak for **2** is at 330 nm, while that for **4** is at 340 nm. Because these peaks are relatively broad, care would be necessary in using this difference to assign structure.

The highly different tlc R_f values distinguish between *N*-methylisocorytuberine and magnoflorine, as do differences in nmr. Magnoflorine does not have a methoxy group in either of the hindered C–1 or C–11 positions and hence shows ^1H nmr resonances in the 3.8 ppm region and ^{13}C nmr resonances at 56.29 and 56.95 (5). The high field (3.45 ppm) ^1H nmr resonance of N-methylisocorytuberine is characteristic of a methoxy in the shielded C–11 position. In the ^{13}C spectrum, the opposite effect is observed, with a low field resonance (60.97 ppm) observable for the methoxy at C–11 in N-methylisocorytuberine.

EXPERIMENTAL SECTION

Details of the synthesis not given below are available in a thesis (4). Intermediates early in the synthesis were identified chiefly by ^1H nmr and ^{13}C spectra. Most were carried along to a subsequent step without rigorous purification.

3-Hydroxy-4-methoxybenzaldehyde (isovanillin) was benzylated according to Uff (6) and converted to 7-benzyloxy-6-methoxyisoquinoline (7) by a modification (7) of the Pomeranz-Fritsch reaction.

3-Benzyloxy-4-methoxybenzaldehyde (6.28 g) and a 10% excess of aminoacetaldehyde dimethylacetal were allowed to reflux in benzene (Dean-Stark trap) until the stoichiometric amount of water had been collected. Washing with hexane provided the imine as a white solid: mp 81.5°–83.5°C; nmr ($CDCl_3$) 3.37 (s, 6H, $-CH(OMe)_2$), 3.73 (d, 2H, $N-CH_2-$, $J=5Hz$), 3.87 (s, 3H, $-OCH_3$), 4.64 (t, 1H, $CH-CH(OMe)_2$, $J=5Hz$), 5.15 (s, 2H, $-OCH_2Ph$), 6.87 (d, 2H,

J=8Hz), 7.13–7.53 (m, 7H, Ar), 8.17 (s, 1H, -CH=N); ir (KBr) 1652 (C=N) cm^{-1}. The imine was reduced to the amine using 1% by weight platinum (IV) oxide in ethanol solution at 50 psi hydrogen in a Parr apparatus. Filtration and evaporation gave a light yellow oil: nmr ($CDCl_3$) 1.55 (s, 1H, -NH), 2.68 (d, 2H, -NH-CH_2-CH(OMe)$_2$, J=5Hz), 3.30 (s, 6H, -CH(OMe)$_2$), 3.68 (s, 2H, -CH_2NH-), 3.82 (s, 3H, -OCH_3), 4.43 (t, 1H, -NH-CH_2-CH(OMe)$_2$, J=5Hz), 6.83–6.92 (m, 3H), 7.23–7.50 (m, 5H, Ar); ir (neat) 3360 (N-H); 1615 and 1600 (Ar) cm^{-1}. The amine was reacted with p-toluenesulfonyl chloride in pyridine to yield the tosylate. A yellowish solid was isolated: mp 49°-51°C; nmr ($CDCl_3$) 2.37 (s, 3H, -CH_3), 3.15 (d, 2H, -CH_2CH(OMe)$_2$, J=5Hz), 3.17 (s, 6H, -CH(OMe)$_2$), 3.80 (s, 3H, -OCH_3), 4.30 (t, 1H, -CH_2CH-(OMe)$_2$, J=5Hz), 4.37 (s, 2H, -CH_2-N), 4.97 (s, 2H, -OCH_2Ph), 6.73 (s, 3H, Ar), 7.17–7.47 (m, 7H, Ar), 7.70 (d, 2H, J=8Hz). The tosylate was dissolved in 75 ml of peroxide free dioxane and 15 ml of 6 N hydrochloric acid. The solution was allowed to reflux for 6 hr in the dark under a nitrogen atmosphere. Evaporation yielded a residue which was chromatographed on Si gel [chloroform-methanol (25:1)] to provide 7-benzyloxy-6-methoxyisoquinoline (**7**): mp 150°–153°C; ^{1}H-nmr ($CDCl_3$) 3.80 (s, 3H, -OCH_3), 5.02 (s, 2H, -OCH_2Ph), 6.76 (s, 1H, H-5 or H-8), 6.94 (s, 1H, H-8 or H-5), 7.00–7.28 (m, 6H, Ar), 8.07 (d, 1H, H-3, J=6Hz), 8.66 (s, 1H, H-1); ^{13}C-nmr ($CDCl_3$) 55.82, 70.47, 104.93, 106.85, 118.90, 124.30, 127.08, 127.83, 128.36, 132.24, 135.86, 141.61, 148.97, 149.61, 152.97 ppm; ir ($CHCl_3$) 1627 (-CH=N-), 1502, 1480, 1250, 1145, 865 cm^{-1}; mass spectrum M^+ 265.1134, calc. for $C_{17}H_{15}NO_2$: 265.1137.

To 2.0 g (7.54 mmol) of 7-benzyloxy-6-methoxyisoquinoline in a mixture of 15 ml CH_2Cl_2, 1.77 g (27.1 mmol) NaCN and 3.5 ml of H_2O was added 1.75 ml (15.1 mmol) of benzoyl chloride with vigorous stirring. After 4 hr of stirring, the organic phase was separated and evaporated to dryness; the residue, when crystallized from ethanol, yielded 1.67 g (4.22 mmol; 56% yield) of 2-benzoyl-7-benzoxy-1-cyano-1,2-dihydro-6-methoxyisoquinoline (**8**) mp 150–153°. Anal. Calcd. for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07. Found: C, 75.60; H, 4.89; N, 7.04.

A mixture of 0.81 g (1.77 mmol) of **8** and 0.78 g (2.65 mmol) of 4-benzyloxy-3-methoxy-2-nitrobenzyl chloride, **9**, (4) in 45 ml DMF was added to 0.126 g (3 mmol) NaH in 5 ml DMF stirred in an N_2 atmosphere (8). External cooling was maintained by an ice bath. Water was added to the solution, which was then extracted with benzene. Evaporation of the benzene left a yellow oil which was used directly for the next step. The oil was dissolved in 25 ml of DMF and stirred under N_2, and 1.4 ml of 40% benzyltrimethylammonium hydroxide (Triton B) in MeOH was added. After 30 min of stirring, 2 ml of conc HCl was added: the ppt which formed was washed with ice water and Et_2O. Crystallization from ethanol yielded 0.72 g (1.34 mmol; 75.6%) of 1-(4-benzyloxy-3-methoxy-2-nitrobenzyl)-7-benzyloxy-6-methoxyisoquinoline, **10**, mp 154.5–155°. Anal. Calcd. for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26; N, 5.22. Found: C, 71.37; H, 5.23; N, 4.98. The isoquinoline **10** was converted to the methiodide **11** in quantitative yield with CH_3I in DMF.

Reduction of **11** to **12** was done in two steps ($CoCl_2$ and $NaBH_4$, followed by H_2/PtO_2) or in one step directly with H_2/PtO_2. Overall yields (40–50%) of **12** were similar (4). Synthesis of **4** and **5** was most easily accomplished without isolation of **12** as follows. Methiodide **11** (0.62 g, 0.91 mmol) in 15 ml of ethanol with 0.07 g of PtO_2 was hydrogenated at 50 psi for 24 hours. The solution was filtered and evaporated to dryness. The residue of **12** was dissolved in 1 ml of conc HCl and 15 ml of H_2O. The solution was cooled in an ice bath under an argon atmosphere; 0.1 g of $NaNO_2$ in 2 ml of H_2O was added and the mixture stirred for 1 hr. Excess sulfamic acid was added, and the mixture was stirred overnight. The mixture was then heated on a steam bath for 15 min and excess zinc dust was added. Heating was continued for an additional 15 min, after which the solution was cooled, made basic with NH_4OH and extracted with chloroform. The chloroform layer was dried and evaporated; the residue was chromatographed [Si gel; ethyl acetate-methanol (5:1)] to yield 0.021 g (0.041 mmol, 4.5% yield) of 1,10-dibenzyloxy-2,11-dimethoxyaporphine (**13**): nmr ($CDCl_3$) 2.57 (s, 3H, NCH_3), 2.7–3.3 (m, 7H), 3.75 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 4.73 (bs, 1H, -O-HCH-Ph), 4.83 (bs, 1H, -O-HCH-Ph), 5.09 (bs, 2H, -OCH_2Ph), 6.67 (s, 1H, H-3), 6.80 (s, 2H, H-8 and H-9), 7.03 (bs, 5H, Ar), 7.17–7.5 (m, 5H, Ar); UV (EtOH) λmax 304 (sh), 274, 226 (sh), 214 nm.

Compound **13** (0.019 g, 0.037 mmol) was dissolved in 1 ml of toluene and 5 mg of 6 N hydrochloric acid. The solution was heated at reflux for 45 min, cooled, and then extracted with chloroform. The acidic aqueous phase was made basic with NH_4OH and then extracted with chloroform. The chloroform extract when evaporated gave (±)-isocorytuberine (**5**) 0.010 g (0.032 mmol, 86% yield): nmr ($CDCl_3$) 2.56 (s, 3H, NCH_3), 2.5–3.2 (m, 7H), 3.68 [s, 3H, (C-11 -OCH_3)], 3.91 [s, 3H, (C-2, -OCH_3)], 6.66 (s, 1H, H-3), 6.85 (d, 1H, H-9, J=8 Hz), 7.01 (d, 1H' H-8, J=8 Hz); uv (EtOH) λmax 307, 297 (sh), 273, 266, 234 nm; ms, M^+ 327, 296, 295, 279, 149.

Compound **13** (0.020 g, 0.039 mmol) was dissolved in 1 ml of DMF, and 1 ml of CH_3I was added. The solution was heated at reflux for 5 hr, and then the excess CH_3I and DMF were removed. Si gel chromatography ($CHCl_3$) provided 0.018 g (0.027 mmol, 71% yield) of methiodide **14**: nmr ($CDCl_3$) 3.08 (s, 3H, -NCH_3), 3.63 (s, 3H, -NCH_3), 3.3–3.8 (m, 7H), 3.70 (s, 3H, -OCH_3), 3.88 (s, 3H, -OCH_3), 4.77 (s, 1H, -O-HCH-Ph), 4.82 (s, 1H, -O-HCH-Ph) 5.02 (s, 2H, -OCH_2Ph), 6.70 (s, 1H, H-3), 6.78–7.08 (m, 7H, Ar), 7.18–7.35 (m, 5H, Ar).

Compound **14** (0.018 g, 0.027 mmol) was dissolved in 5 ml of 6 N hydrochloric acid and heated at reflux for 3 hr. Si gel chromatography [methanol-water-ammonium hydroxide solution (15:3:1)] provided 0.010 g (80% yield) of semisolid isocorytuberine methiodide **4**: ms: 341.1613 (M^+-1: Calc. for $C_{21}H_{23}NO_4$ 341.1627; the M^+ 342 peak was of insufficient intensity for exact mass measurement). Other spectral data are in table 1 except: ^{13}C-nmr (CH_3OD) 154.50, 150.82, 144.75, 143.35, 125.13, 124.38, 121.63, 120.87, 120.41, 120.17, 118.07, 110.77, 69.84, 61.32, 60.97, 55.71, 53.38, 43.10, 30.43, 23.89 ppm.

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